because of recurring RCC, then chronic hemodialysis three times weekly was started. Diagnoses of recurrence with metastasis were carried out for the two patients. First-line sunitinib achieved disease control for 2 and 4 years, respectively. As a second-line treatment, the patients were given everolimus with a starting dose of 5 mg/day and there is a possibility of escalation according to the tolerance after first everolimus PKs assessment. Patient 1 experienced escalation to 10 mg/day but required dose reduction to 5 mg/day due to grade (gr) 3 asthenia, gr 2 diarrhea, and gr 2 mucitis. Patient 2 could not receive 10 mg/day because of adverse events such as gr 3 hyperglycemia, gr 2 asthenia, and gr 2 mucitis. The HD was carried out with a dialyzer using either a polyethersulphone (patient 1) or polymethyl-methacrylate (patient 2) membrane (surface area 1.6 m²) with a dialysate and blood flow rates constant at 700 and 350 ml/min. At 3 months, patients 1 and 2 experienced disease progression and were diagnosed with gr 2 pneumonitis.

Blood samples were taken after reaching the steady state and just before HD, then during (together with a dialysate) and after the end of HD. Everolimus was measured using a validated LC/MS-MS method [2]. Briefly, patient’s samples (together with standards and controls) were spiked with an internal standard, then subjected to protein precipitation with ZnSO₄, and extracted by acetonitrile. The range of quantification of the method is between 1 and 100 ng/ml. For everolimus measurement in a dialysate, acetonitrile was added to the samples and the concentrations were assessed using dialysate buffer-based spiked standards. As described in Figure 1, HD did not modify the blood everolimus concentrations as they were close to the predialysis level. Moreover, no everolimus was detected in the dialysate, confirming its lack of adhesion to the dialysis membrane.

Here are the first published data evaluating the impact of HD on everolimus PKs. Our results suggest that there is no influence of HD on everolimus blood concentrations. This is probably related to the absence of diffusion of everolimus in the dialysate. Interestingly, the membranes used are common and represent around 90% of the membranes used in routine for HD. Our two patients experienced significant toxic effects and none of them could receive the approved dosage of 10 mg/day. Even if it appears useless to modify everolimus dosing for patients treated in the context of mRCC and needing HD, this should be confirmed with a higher number of patients. The toxic effects observed do not seem to be linked to an overdose of everolimus, thus careful follow-up should be recommended in the setting of HD patients.

A. Thiery-Vuillemin 1,2,4,* , E. Curtit4, T. Maurina4, D. Montange5, C. Succi5, T. NGuyen5, S. Kim6, F. Montcuquet4, X. Pivot1,2,3 & B. Royer1,3
1INSERM, UMR1098, Besançon
2UMR1098, SFR IBCT, University of Franche-Comté, Besançon, France
3Pharmacology Unit, CHU Minjoz, Besançon
4Medical Oncology Unit, CHU Minjoz, Besançon; 5Osmose Franche Comté, Besançon, France
(*E-mail: a.thieryvuillemin@mac.com)

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references

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Meat consumption and cancer risk: is the definition of red meat always suitable?

We read with interest the article of Keszei et al. [1], who concluded that processed as well as red meat intake was positively associated with esophageal squamous cell carcinoma in men, showing hazard ratios of 3.47 and 2.66, respectively, for the highest versus lowest quintile of processed and red meat. It is noteworthy, however, that in the Netherlands Cohort study, red meat was defined as beef, pork, minced meat (both beef and pork), liver, and other non-poultry meats (e.g. horsemeat and lamb).

We believe that the generalization of all types of ‘red meat’ under this definition might be somehow inappropriate in clinical studies. Horsemeat, which is notably the ‘most red’ among all meats due to the large myoglobin content, differs widely from other types of red meat, especially in terms of composition and content of potential carcinogens. It has been proven, in fact, that the nutritional characteristics of horsemeat are highly favourable in comparison to those of beef and pork. While containing similar levels of proteins, horsemeat has a

![Figure 1. Evolution of everolimus concentrations with time during hemodialysis (HD). The dosage of everolimus was 10 mg daily for patient 1 (circles) and 5 mg daily for patient 2 (squares). T0 samples are predialysis concentrations.](image-url)
higher content of some ‘anti-cancerogenic’ substances such as palmitoleic and monounsaturated fatty acids, retinol, low levels of fat (especially cholesterol) and high unsaturated fatty acids, thus favourably impacting on the cardiovascular risk as well [2]. Another likely difference between horsemeat and beef or pork is that the latter is more largely consumed as manufactured and processed products, which are thereby more susceptible to the introduction of preservative that may generate cancer promoting substances such as N-nitroso compounds [3].

The consumption of horsemeat is relatively high in some countries, and is also considered a delicacy in others. With the price of beef increasing, horsemeat might be a viable alternative also in those countries that have for long considered eating horses as a taboo. Since consumption of horsemeat may be healthier than regularly eating beef or pork for a less negative impact on cancer and cardiovascular risk, we believe that it may be important that the potential carcinogenic effects of the different red meats should be separately assessed.

G. Lippi1,* & C Mattiuzzi2

1Clinical Chemistry and Haematology Laboratory, Department of Pathology and Laboratory Medicine, Academic Hospital of Parma and 2Service of Clinical Governance, Hospital of Trento, Italy

*(E-mail: glippi@ao.pr.it)

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